REMARKS

Claims 1–20 are pending in the instant application. With this Amendment, Applicants have canceled claims 1–20 and presented new claims 21–55, all of which are supported by the application as filed. For example, the dosage and duration limitations in claims 21 and 30 are supported by the specification as filed at page 6, lines 21–25. Furthermore, application of a nasal spray formulation at the applicable dosage and for the applicable duration is described in the examples on pages 12–22 of the application as filed. Additionally, the formulation as nasal spray and nasal drops is mentioned at page 9, lines 23-24. Finally, the administration of the drug before meals is described in the specification as filed at page 6, lines 1–2.

Accordingly, no new matter has been introduced by way of these amendments and entry thereof is respectfully requested. A copy of all pending claims after entry of this amendment is presented in Appendix B, attached hereto.

Applicants reserve the right to further prosecute the subject matter of claims 1 – 20 in one or more continuation or divisional applications.

Applicants have also carried out a number of minor amendments to the specification for the purpose of correcting minor typographical and grammatical errors that would be apparent to an ordinary reader. Marked up versions of amended paragraphs of the specification showing changes made therein are presented in Appendix A, attached hereto.

Applicants have carefully considered the Examiner's office action, mailed February 14, 2002 and respectfully request consideration of the remarks herein.

Rejections under § 112

Claims 2–11 and 17–20 were rejected under 35 U.S.C. § 112 ¶ (2) as allegedly being indefinite because they lacked proper antecedent basis for the limitation "daily dosage." Claims 21 and 30, from which all pending claims now depend, contain the term "daily dosage" and therefore the Examiner's rejection is no longer relevant.

Claim 17 was rejected under 35 U.S.C. § 112 ¶(2) as allegedly being indefinite for containing a range in a range. Claim 48 has now been presented, in which ranges in

parentheses are absent; dependent claims 49–55 include the ranges formerly presented in Claim 17.

Claim 18 contained a typographical error, in the range "about 1 week to about 8 weeks." No pending claim recites the same limitation, thus mooting the Examiner's rejection.

Accordingly, Applicants respectfully request that the Examiner withdraw the rejections of record under 35 U.S.C. § 112 ¶(2).

Rejections under § 103(a)

The Examiner has rejected all pending claims under 35 U.S.C. § 103(a) as allegedly being obvious over one or more cited references. The Applicants remind the Examiner that, in order to make out a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references or in the knowledge available to one of ordinary skill in the art to modify the reference or to combine the reference teachings and that there must be some reasonable expectation of success. The teaching or suggestion and the expectation of success must both be found in the prior art and not based on Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991).

In particular, the Examiner rejected claims 1–12 and 15–17 under 35 U.S.C. § 103(a) as allegedly being obvious over "Marketing Authorization for Pramidin" ("Pramidin"). Upon entry of the claims filed herewith, all pending claims have either the limitation that metoclopramide is administered intranasally for about 2 weeks to about 8 weeks, or an intervening time period, or the limitation that metoclopramide is administered intranasally at a daily dosage of between about 40 mg/day and about 160 mg/day. Accordingly, Applicants respectfully traverse the rejection.

Pramidin does not teach administering metoclopramide intranasally for periods as long as about 2 weeks to about 8 weeks. In particular, Pramidin is silent in respect of a recommended duration of treatment for gastroparesis. Accordingly, one of ordinary skill in the art would have obtained no guidance or suggestion from Pramidin as to the recited period of time over which to administer metoclopramide intranasally.

Furthermore, Pramidin neither teaches nor suggests administering metoclopramide intranasally for the treatment of symptoms of gastroparesis in amounts in excess of 30 mg/day. In fact, although Pramidin specifies larger doses of intranasal metoclopramide for treatment of hyperemesis conditions of iatrogenic origin, including other disorders such as chemotherapy-induced acute hyperemesis and post-surgical nausea, the dosages taught for treatment of gastroparesis are significantly lower (*e.g.*, 20-30 mg/day) than those taught for the other indications. Thus, one of ordinary skill in the art would assume that the different dosages for different disorders, as reported in Pramidin, had been selected for reasons of efficacy. Accordingly, one of skill in the art would not have been motivated to modify the teachings of Pramidin for gastroparesis in order to arrive at Applicants' dosages for gastroparesis but instead would have assumed that the dosages reported in Pramidin were adequate. Therefore, Applicants respectfully request the Examiner to remove the rejection of record.

The Examiner has also rejected claims 1–20 under 35 U.S.C. § 103(a) as allegedly being obvious over "Robins" (product information on Reglan®), in view of U.S. patent no. 4,624,965 ("Wenig"). Applicants respectfully traverse the rejection, in particular because Wenig does not teach or suggest a nasal spray or drop formulation meeting the limitations of Applicants' claims.

Applicants' pending claims are directed to a nasal formulation of metoclopramide, as a spray or drops, for treatment of symptoms of gastroparesis. Furthermore, as discussed hereinabove, Applicants' pending claims recite either that metoclopramide is administered intranasally for about 2 weeks to about 8 weeks, or an intervening time period, or that metoclopramide is administered intranasally at a daily dosage of between about 40 mg/day and about 160 mg/day. Reglan teaches oral or injectable forms of metoclopramide for treatment of gastroparesis. However, Wenig is silent as to the merits of metoclopramide for the specific treatment of gastroparesis. Furthermore, Wenig teaches no protocol for administering either nasal spray or drop formulation for treatment of symptoms in humans. By which is meant that Wenig teaches neither duration nor dosing of a spray or drop formulation for intranasal application to humans. In particular, Examples 2–5 of Wenig teach application of metoclopramide (MCP) or metoclopramide hydrochloride (MCP.HCl) in nasal

drops to animals; Example 7 demonstrates toxicity studies of a gel formulation of MCP on rabbits; and Examples 8 and 9 show the application of MCP.HCl gel formulations to humans.

Furthermore, the dosages taught by Wenig for application to humans (5 and 10 mg, and 20 mg in Example 8, and 40 mg in Example 9) do not teach one of skill in the art the applicable therapeutically effective dosages for a nasal spray or drop formulation. Moreover, Examples 8 and 9 of Wenig do not provide one of skill in the art with sufficient guidance to devise a duration of treatment for relieving the symptoms of gastroparesis.

Accordingly, one of skill in the art would not have been motivated to combine the teachings of Robins and Wenig in order to arrive at Applicants' claimed invention and Applicants respectfully request that the Examiner remove the rejection of record.

Additionally, the Examiner has also rejected claims 1–20 under as 35 U.S.C. § 103(a) as allegedly being obvious over "Robins" (product information on Reglan®) in view of U.S. patent no. 5,760,086 ("Psilogenis"). Applicants respectfully traverse the rejection.

Psilogenis is directed towards nasal administration of MCP for treatment of delayed onset emesis, particularly emesis induced by chemotherapy. Psilogenis does not teach efficacy of a nasal spray or drop formulation for treatment of gastroparesis. Furthermore, Psilogenis does not teach that metoclopramide can be safely administered intranasally for longer than a week. Thus, Psilogenis provides no guidance for appropriate dosages and treatment times for intranasally administered metoclopramide in the treatment of gastroparesis. Furthermore, Psilogenis does not teach administration of metoclopramide intranasally in dosages greater than about 120 mg/day. Accordingly, one of ordinary skill in the art would not have looked to Psilogenis for the teachings that are absent from Robins in respect of an appropriate intranasal formulation and duration of treatment for relieving symptoms of gastroparesis. Therefore, Applicants respectfully request the Examiner to withdraw the rejection of record.

Conclusion

Applicants respectfully request that the above remarks be made of record in the file history of the present application. It is respectfully submitted that Claims 21–55, as presented

herein, meet all of the requirements for patentability and are in condition for allowance or appeal. An early indication of allowance is, therefore, kindly solicited.

No additional fees are believed due with this response. However, should the Commissioner determine otherwise, he is hereby authorized to charge any fees associated with filing this Response to Pennie & Edmonds LLP Deposit Account No. 16-1150. A copy of this sheet is enclosed.

Date: August 14, 2002

Richard G. A. Bone

Richard G. A. Bone, Ph.D.
Limited Recognition Under 37 C.F.R. § 10.9 (b)
(Copy of Certificate Enclosed)

for: Brian M. Poissant, (Reg. No. 28,462.)
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No additional fees are believed due with this response. However, should the Commissioner determine otherwise, he is hereby authorized to charge any fees associated with filing this Response to Pennie & Edmonds LLP Deposit Account No. 16-1150. A copy of this sheet is enclosed.

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APPENDIX A:
CHANGES TO THE SPECIFICATION
UPON ENTRY OF THE AMENDMENT UNDER 37 C.F.R. § 1.111
FILED 14 AUGUST 2002

U.S. PATENT APPLICATION SERIAL NO. 09/821,139
(ATTORNEY DOCKET NO. 7960-131)

The following mark-up scheme is adopted:
Deleted material: ~~Strike-through~~
Inserted material: **Bold Underline**

Please revise the paragraph beginning at page 9, line 28, and ending at page 10, line 2, as follows:

A typical MCP nasal formulation is in solution form having a light amber color and being non-cloudy to the naked eye with an pH of between about 3.0-5.0. The typical formulation may contain benzyl alcohol of at least about 13.5 mg/ml containing practically no impurities as determined by high pressure liquid chromatography (HPLC) and having a bacterial count of less than 250 ufc/ml and free of pathogens sufficient to form an acceptable pharmaceutical nasal spray dosage form. The solvent ~~is maybe~~ **may be** purified water suitable for use in nasal dosage forms or any equivalent water (*e.g.* injectable water) that is allowed for use in such nasal dosage forms. *See* REMINGTON'S PHARMACEUTICAL SCIENCES, any edition from 1980-1996. For the adequate and/or sufficient treatment and control of gastroparesis, a typical dose is that dose which is therapeutically effective and which minimizes side-effects and drug interactions.

Please revise the paragraph beginning at page 10, line 29, and ending at page 10, line 36, as follows:

Various techniques may be used to ~~access~~ **assess** the severity of the gastroparesis and gastric emptying. Methods well known in this art include, for example, questioning the patient on symptoms related to the disease as well as techniques such as radioscintigraphy, ultrasonography, and techniques using radiopaque markers such as barium. Radioscintigraphy appears to be the preferred method, due to its relatively high sensitivity and specificity, ease of use, and low exposure to radiation. All of these methods can be

used to determine, together with teachings of the present invention, the appropriate dosage for a particular patient.

Please revise the paragraph beginning at page 11, line 1, and ending at page 11, line 8, as follows:

The weight of the patient may also affect the dosage to be administered. Typically, a dose of between about 0.1 mg/kg to about 2.5 mg/kg is given to ~~an~~ a patient suffering from gastroparesis. The dosages can be either about 0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg, 0.4 mg/kg, 0.5 mg/kg, 0.6 mg/kg, 0.7 mg/kg, 0.8 mg/kg, 0.9 mg/kg, 1.0 mg/kg, 1.1 mg/kg, 1.2 mg/kg, 1.3 mg/kg, 1.4 mg/kg, 1.5 mg/kg, 1.6 mg/kg, 1.7 mg/kg, 1.8 mg/kg, 1.9 mg/kg, 2.0 mg/kg, 2.1 mg/kg, 2.2 mg/kg, 2.3 mg/kg, 2.4 mg/kg, 2.5 mg/kg. A preferred nasal dosage is between about 0.06 to about 1.2 mg/kg of body weight. Other preferred nasal dosages are about .06 mg/kg, .08 mg/kg, 1.0 mg/kg, 1.2 mg/kg and 1.4 mg/kg.

Please revise the paragraph beginning at page 11, line 10, and ending at page 11, line 33, as follows:

The expected benefit of an intranasal formulation of metoclopramide for gastroparesis is to provide an alternative route of administration for this agent to patients who have uncomfortable gastrointestinal symptoms of gastroparesis. The intranasal formulation of metoclopramide will spare patients with active symptoms the potential additional discomfort of having to swallow an oral formulation and serves as an alternative to injectable formulations. As presented in greater detail below in Section 6, the nasal administration of metoclopramide treatment of gastroparesis offers many benefits, some of which are unexpected. For example, as illustrated below, one unexpected benefit is that while patents receiving the nasal form of the drug were exposed to less drug overall, 10 mg of nasal metoclopramide was superior to 10 mg oral metoclopramide in reducing symptoms with particular significance in the categories of feeling full after eating and persistent fullness. Further, less exposure to metoclopramide reduces the opportunity for central nervous system (CNS) side effects (*see* the data relating to $AUC_{o\text{-}inf}$ for 10 mg oral versus nasal). Also, the benefit of the 20 mg nasal (80 mg/day) was superior than 10 mg oral ~~in~~

for all symptoms studied and was well tolerated for six weeks. In contrast, 80 mg/day of oral metoclopramide would be expected to result in significant CNS side effects and is not indicated for such duration. However, nasal doses of 80 mg/day were well tolerated for an extended period of six weeks. Further, because of its rapid onset of action (*see* Figures 2B and 2C showing higher initial blood levels, *i.e.,* faster absorption), nasal metoclopramide may be substituted for intravenous administration in patients with severe gastroparesis for whom the oral form is not indicated. The benefits of nasal administration over intravenous administration being obvious to the skilled practitioner. In sum, the nasal form of metoclopramide, as demonstrated herein, provides heretofore unexpected benefits in the treatment of gastroparesis.

APPENDIX B
ENTIRE SET OF PENDING CLAIMS
UPON ENTRY OF THE AMENDMENT UNDER 37 C.F.R. § 1.111
FILED 14 AUGUST 2002

U.S. PATENT APPLICATION SERIAL NO. 09/821,139
(ATTORNEY DOCKET NO. 7960-131)

21. (New) A method for treating or reducing the symptoms of gastroparesis in a patient comprising:

administering metoclopramide or a pharmaceutically acceptable salt thereof to a patient in need of gastroparesis treatment, wherein said metoclopramide is in a pharmaceutically acceptable nasal spray formulation and administered intranasally in a therapeutically effective amount at a daily dosage for about 2 weeks to about 8 weeks, so that one or more symptoms of gastroparesis is reduced.

22. (New) The method of claim 21 wherein said daily dosage is administered for about 5 weeks to about 8 weeks.

23.(New) The method of claim 21 wherein said daily dosage is administered for about 6 weeks.

24. (New) The method of claim 21 wherein said daily dosage is between about 40 mg/day and about 160 mg/day.

25. (New) The method of claim 24 wherein said daily dosage is between about 40 mg/day and about 80 mg/day.

26. (New) The method of claim 24 wherein said daily dosage is about 40 mg/day.

27. (New) The method of claim 24 wherein said daily dosage is about 80 mg/day.

28. (New) The method of claim 21 wherein said daily dosage is between about 0.1 mg/kg to about 2.5 mg/kg.

29. (New) The method of claim 28, wherein said daily dosage is between about 0.6 mg/kg to about 1.2 mg/kg.

30. (New) A method for treating or reducing the symptoms of gastroparesis in a patient comprising:

administering metoclopramide or a pharmaceutically acceptable salt thereof to a patient in need of gastroparesis treatment, wherein said metoclopramide is in a pharmaceutically acceptable nasal formulation and administered intranasally as a spray or drops in a therapeutically effective amount at a daily dosage of between about 40 mg/day and about 160 mg/day, so that one or more symptoms of gastroparesis is reduced.

31. (New) The method of claim 30 wherein said daily dosage is between about 40 mg/day and about 80 mg/day.

32. (New) The method of claim 30 wherein said daily dosage is about 40 mg/day.

33. (New) The method of claim 30 wherein said daily dosage is about 80 mg/day.

34. (New) The method of claim 30 wherein said daily dosage is between about 0.1 mg/kg to about 2.5 mg/kg.

35. (New) The method of claim 34, wherein said daily dosage is between about 0.6 mg/kg to about 1.2 mg/kg.

36. (New) The method of claim 30 wherein said daily dosage is administered for about 2 weeks to about 8 weeks.

37. (New) The method of claim 30 wherein said daily dosage is administered for about 5 weeks to about 8 weeks.

38. (New) The method of claim 1 wherein said daily dosage is administered for about 6 weeks.

39. (New) The method of claims 21 or 30 wherein said daily dosage is divided into 3 or 4 equal smaller doses and administered at equally spaced intervals within 24 hours.

40. (New) The method of claim 39 wherein the smaller doses are about 10 mg each.

41. (New) The method of claim 39 wherein the smaller doses are about 20 mg each.

42. (New) The method of claims 21 or 30 wherein said daily dosage is divided into 3 or 4 equal smaller doses and administered before meals.

43. (New) The method of claim 42 wherein said doses are administered before meals and before bedtime.

44. (New) The method of claim 42 wherein the smaller doses are about 10 mg each.

45. (New) The method of claim 42 wherein the smaller doses are about 20 mg each.

46. (New) The method of claims 21 or 30 wherein the metoclopramide or pharmaceutically acceptable salt thereof is in an aqueous-based carrier.

47. (New) The method of claims 21 or 30 wherein the metoclopramide or pharmaceutically acceptable salt thereof is in a sustained release formulation.

48. (New) The method of claims 21 or 30 wherein the metoclopramide or pharmaceutically acceptable salt thereof is co-administered with one or more additional drugs.

49. (New) The method of claims 21 or 30 wherein said dosage is administered for treating gastroparesis caused by any of: diabetes, a postviral syndrome, anorexia nervosa, surgery on the stomach or vagus nerve, a medication, gastroesophageal reflux disease, smooth muscle disorder, a nervous system disease, or a metabolic disorder.

50. (New) The method of claim 49 wherein said dosage is administered for treating gastroparesis caused by diabetes.

51. (New) The method of claim 50 wherein said diabetes is selected from the group consisting of type 1 diabetes and type 2 diabetes.

52. (New) The method of claim 49 wherein said medication is selected from the group consisting of: anticholinergics, and narcotics which slow contractions in the intestine.

53. (New) The method of claim 49 wherein said smooth muscle disorder is selected from the group consisting of: amyloidosis and scleroderma.

54. (New) The method of claim 49 wherein said nervous system disease is selected from the group consisting of: abdominal migraine and Parkinson's disease.

55. (New) The method of claim 49 wherein said metabolic disorder is hypothyroidism.